Timing of Decompressive Surgery of Spinal Cord after Traumatic Spinal Cord Injury: An Evidence-Based Examination of Pre-Clinical and Clinical Studies

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Abstract

While the recommendations for spine surgery in specific cases of acute traumatic spinal cord injury (SCI) are well recognized, there is considerable uncertainty regarding the role of the timing of surgical decompression of the spinal cord in the management of patients with SCI. Given this, we sought to critically review the literature regarding the pre-clinical and clinical evidence on the potential impact of timing of surgical decompression of the spinal cord on outcomes after traumatic SCI. The primary literature search was performed using MEDLINE, CINAHL, EMBASE, and Cochrane databases. A secondary search strategy incorporated articles referenced in prior meta-analyses and systematic and nonsystematic review articles. Two reviewers independently assessed every study with regard to eligibility, level of evidence, and study quality. Of 198 abstracts of pre-clinical studies, 19 experimental studies using animal SCI models fulfilled our inclusion and exclusion criteria. Despite some discrepancies in the results of those pre-clinical studies, there is evidence for a biological rationale to support early decompression of the spinal cord. Of 153 abstracts of clinical studies, 22 fulfilled the inclusion and exclusion criteria. While the vast majority of the clinical studies were level-4 evidence, there were two studies of level-2b evidence. The quality assessment scores varied from 7 to 25 with a mean value of 12.41. While 2 of 22 clinical studies assessed feasibility and safety, 20 clinical studies examined efficacy of early surgical intervention to stabilize and align the spine and to decompress the spinal cord; the most common definitions of early operation used 24 and 72 h after SCI as timelines. A number of studies indicated that patients who undergo early surgical decompression can have similar outcomes to patients who received a delayed decompressive operation. However, there is evidence to suggest that early surgical intervention is safe and feasible and that it can improve clinical and neurological outcomes and reduce health care costs. Based on the current clinical evidence using a Delphi process, an expert panel recommended that early surgical intervention should be considered in all patients from 8 to 24 h following acute traumatic SCI.

Key words: animal studies; clinical research; spinal cord injury; systematic review; timing of surgery

Introduction

TRAUMATIC SPINAL CORD INJURY (SCI) is a potentially catastrophic event for individuals who develop motor, sensory, and autonomic deficits and for society due to the economic burden. Currently, the management of individuals with acute SCI includes pharmacological agents and surgical intervention. The most promising pharmacological therapies

include drugs that, in pre-clinical studies, improved axonal conduction, antagonized excitatory amino acid antagonists, blocked potassium and sodium channel, and attenuated extracellular myelin mediator growth inhibitory proteins (Baptiste and Fehlings, 2007).

Surgical intervention is indicated for decompression of the spinal cord in addition to realignment and stabilization of the spine. Although the recommendations for spine surgery in

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specific cases of acute traumatic SCI are well recognized, there is considerable uncertainty regarding the role of the timing of surgical decompression of the spinal cord in the management of patients with SCI.

Given this background, we sought to critically review the literature with regard to the pre-clinical and clinical evidence on the potential impact of timing of surgical decompression of the spinal cord on outcomes after traumatic SCI.

Methods

This study comprehensively reviews the pre-clinical and clinical evidence for early surgical decompression of the spinal cord in patients after traumatic SCI. Moreover, this systematic review is focused on the following three key questions:

1. Is there pre-clinical evidence for biological benefits of early surgical decompression in animal SCI models?
2. What is the optimal timing for surgical decompression of the spinal cord based on the current clinical evidence?
3. What are the potential effects of early decompression of the spinal cord on the clinical, neurological, and functional outcomes in the acute care setting?

For this purpose, we selected all original articles that examined the potential effects of duration of compression or timing of surgical decompression of spinal cord on outcomes in the setting of traumatic SCI. Case reports, editorial articles, and meeting abstracts were excluded.

Literature search strategy

The primary literature search was carried out using MEDLINE, CINAHL, EMBASE, and Cochrane databases. A secondary search strategy incorporated articles referenced in meta-analyses and systematic and nonsystematic review articles that the primary search strategy yielded.

The literature searches targeted publications from 1966 to April 2009. The search strategy included the following specific terms: "surgical decompression," "decompression," "spinal cord compression," "time," and "timing." Those terms were paired with the following Medical Subject Headings (MeSHs): "spinal cord injury," "SCI," "tetraplegia," "quadriplegia," and "paraplegia." The literature search was limited to papers written in English. The search results were divided into pre clinical studies (animal SCI models) and clinical studies.

Data abstraction and synthesis

During the culling process, two reviewers (JCF and VN) independently selected the articles that fulfill the inclusion and exclusion. Disagreements were solved by a debate and consensus between both reviewers.

A research assistant extracted the relevant data from each selected article. Subsequently, both reviewers examined all clinical studies with regard to the extracted data and determined the level of evidence according to Sackett et al. (2000). In addition, both reviewers assessed the methodological quality of each article using the criteria of Downs and Black (1998). Divergences during those steps were solved by consensus between both reviewers. The main results of each article and the reviewers' assessments are summarized in Tables 1 and 2.

Establishment of recommendations

Using the information in the summary tables, the authors answered the previously formulated questions and developed a series of statements. An expert panel was established that consisted of two board-certified neurosurgeon/clinician scientists actively practicing in an academic institution (M.D., Ph.D.), two board-certified neurosurgeons engaged in full clinical practice (M.D.), one neurosurgical resident/clinical research fellow (M.D., Ph.D. candidate), one orthopedic spine surgeon/clinician scientist actively practicing in an academic institution (M.D., Ph.D.), one orthopedic spine surgeon engaged in full clinical practice (M.D.), four spinal cord injury scientists (Ph.D.), one physiotherapist/rehabilitation scientist (Ph.D. candidate), and one clinical epidemiologist (Ph.D.). Each member of the expert panel is a member of one or more professional spine organizations including Spine Trauma Study Group, Acute Practice Network, Spinal Cord Injury Solutions Network, Section of Neurotrauma and Critical Care of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, the North American Spine Society, and AOSpine. The expert panel was provided a copy of this manuscript and sufficient time to review it. The expert panel then convened to discuss the series of statements using a modified Delphi method (Reid, 1993). In essence, this method provided the expert panel with time to discuss the posed series of statements and formulate a recommendation based on the evidence provided in the manuscript. Following discussion, with the authors of this manuscript present to address any questions, the expert panel voted and offered recommendations.

Results

Literature search

Pre-clinical studies. Of 198 abstracts captured in our search, 48 articles were pre-selected to be reviewed by the two reviewers. Of those 48 articles, 19 experimental studies using different animal SCI models fulfilled the inclusion and exclusion criteria of this systematic review (Aki and Toya, 1984; Bohlman et al., 1979; Brodkey et al., 1972; Carlson et al., 1997a, 1997b, 2003; Croft et al., 1972; Delamarter et al., 1991, 1995; Dimar et al., 1999; Dolan et al., 1980; Guha et al., 1987; Hejcl et al., 2008; Kobrine et al., 1978, 1979; Nystrom and Berglund, 1988; Rabinowitz et al., 2008; Thienprasit et al., 1975; Zhang et al., 1993). Extracted data from those 19 pre-clinical studies are summarized in Table 1. In brief, the pre-clinical studies used a spinal cord compression or contusion model in dogs ($n=8$), rats ($n=6$), cats ($n=3$), or monkeys ($n=2$). Outcome measures included electrophysiological testing ($n=12$), behavioral tests ($n=11$), histopathological examination of spinal cord tissue ($n=7$), spinal cord blood flow assessment ($n=4$), and spinal cord concentration of energy-related metabolites ($n=1$). While the majority of the pre-clinical studies compared different time periods of spinal cord compression or contusion, three animal studies reported outcomes of animal SCI models without group comparisons on the timing of spinal cord compression or decompression (Bohlman et al., 1979; Brodkey et al., 1972; Kobrine et al., 1978).

Clinical studies. The primary search of clinical studies yielded 153 abstracts of which three review papers were used

TABLE 1. SUMMARY OF THE CHARACTERISTICS AND RESULTS OF THE PRE-CLINICAL STUDIES ON TIMING OF SURGICAL DECOMPRESSION AFTER SPINAL CORD INJURY

References	Sample features	Outcome measures	Injury model	Timing of decompression	Study conclusions
Brodkey et al. (1972)	<ul style="list-style-type: none"> • N = 5 • Cats • Weight: 2–4.5 kg • Level: low thoracic level 	<p>Mean arterial blood pressure, and CEP.</p> <p>No statistical analysis.</p>	A weight-holding apparatus was positioned so that a predetermined weight would be delivered over the entire dorsal surface of the cord and intact dura.	Time since spinal cord compression and/or aortic clamping to CEP effects.	<ul style="list-style-type: none"> • In two experiments after the CEP had disappeared due to the combined influence of both the weight on the cord and blood pressure reduction, the weight was removed leaving the blood pressure low. • The CEP recordings in each animal returned within 5 min only to disappear again. On one occasion it disappeared 15 min later and on the other occasion 5 min later. • When the blood pressure finally rose to normal levels the CEP promptly returned and did not again disappear when the blood pressure subsequently dropped after about 30 min of normotension. ◦ Graded pressure (38 g for 5–20 min and 48 g for 20 min) on the spinal cord produced reversible blocking of SSEP. ◦ With this type of trauma, block of motor transmission through the cord paralleled the block of sensory transmission, and each seemed to be a sensitive indicator of spinal cord function. ◦ While a compression of 58 g for 20 min produced a profound clinical deficit, 48 g for 20 min produced a severe deficit with early signs of recovery, and 38 g for 20 min produced little clinical deficit.
Croft et al. (1972)	<ul style="list-style-type: none"> • N = 15 • Cats • Weight: 2–4.5 kg • Level: T9–10 	<p>SSEP and behavioral assessment.</p> <p>No statistical analysis.</p>	A weight holding apparatus delivered a predetermined amount of weight over the entire dorsal surface of the cord and intact dura.	<p>18 g for 20 min;</p> <p>28 g for 20 min;</p> <p>38 g for 5 min;</p> <p>38 g for 15 min;</p> <p>38 g for 20 min;</p> <p>48 g for 20 min;</p> <p>58 g for 20 min</p>	
Thienprasit et al. (1975)	<ul style="list-style-type: none"> • N = 28 • Cats • Weight: 2–5 kg • Level: 6 cm cranial from L2 	<p>CER at 5 min, 1 h, 3 h, and 6 h, and behavioral test (5-grade assessment).</p> <p>Statistical analysis was done, but the test used was not specified.</p>	A Fogarty catheter (French n. 3) was passed through a L2 laminectomy extradurally in the cephalic direction for 6 cm. Then, its balloon was instantaneously inflated with 0.6–0.9 cm ³ of air and immediately deflated.	<p>Animals were divided into three groups: (i) no treatment after SCI; (ii) 2–4 level laminectomy at 6 h after SCI; and (iii) 2–4 level laminectomy at 6 h after SCI associated with cooling (saline at 15 ± 2°C) of spinal cord for 2 h.</p>	<ul style="list-style-type: none"> • Animals were divided according to their CER. Group 1 included animals whose CER did not reappear until 6 h after SCI. Group 2 included animals whose CER disappeared at time of SCI but reappeared within 6 h. • Animals in the Group 1 did not recover the ability to walk. • There was no difference between the animals in the Group 1 that were treated with laminectomy and untreated animals in the Group 1 ($p = 0.4$). • In the Group 1, the animals treated with laminectomy and cooling significantly differed from the untreated animals ($p < 0.01$). • In the Group 2, animals had significant neurological recovery regardless of type of treatment. All animals were able to regain the ability to walk. • In the Group 2, there was no difference between the animals that were treated with laminectomy and cooling and untreated animals ($p = 0.4$).
Kobrine et al. (1978)	<ul style="list-style-type: none"> • N = 10 • Monkeys (macaque) • Weight: 3–4.5 kg • Level: T6 	<p>SER, blood flow, and adverse effects.</p> <p>No statistical analysis.</p>	Spinal cord compression using Fogarty catheter in the epidural space lateral to the spinal cord on the right side.	<p>Pumped infusion of 0.15–0.2 mL into the balloon in 1 h followed by immediate deflation of the balloon.</p>	<ul style="list-style-type: none"> • SERs did not disappear until the blood flow in the compressed segment was zero. • In seven animals a post-ischemic hyperemia occurred. • Results suggested that mechanical forces of compression, rather than ischemia are mainly responsible for the loss of neural conduction in such a model.

(Continued)

TABLE 1. CONTINUED

References	Sample features	Outcome measures	Injury model	Timing of decompression	Study conclusions
Kobrine et al. (1979)	<ul style="list-style-type: none"> • N = 18 • Monkeys (macaque) • Weight = 3–4.5 kg • Level: T6 	<p>Spinal cord blood flow and SER.</p> <p>No statistical analysis.</p>	<p>Spinal cord compression using Fogarty catheter (French n. 3) in the epidural space lateral to the spinal cord on the right side.</p>	<p>The balloon was acutely inflated by hand to a volume of 0.25 cm³ and kept inflated for periods of 1, 3, 5, 7, or 15 min followed by immediate deflation of the balloon.</p>	<ul style="list-style-type: none"> ◦ The SER disappeared immediately in all groups upon acute balloon compression. ◦ Animals with compression for 3, 5, 7, and 15 min failed to demonstrate any return of SER during the 1-hour period following deflation. ◦ All animals in the 1-min compression group exhibited return of the SER by 1 h. ◦ The spinal cord blood flow in all animals was either normal or hyperemic by 5 min after deflation and remained so for the remainder of the experiment. ◦ No case of post-compression ischemia was demonstrated. ◦ No-reflow phenomenon was not demonstrated in any groups.
Bohlman et al. (1979)	<ul style="list-style-type: none"> • N = 14 • Dogs (purebred beagle hounds) • Sex: female • Weight: 14 kg • Level: C5–6 	<p>Behavioral test (climbing a 20° inclined plane and modified Tarlov grading), CEP, and histopathological examination.</p> <p>No statistical analysis.</p>	<ul style="list-style-type: none"> • Compression model using a transducer. • Contusion model used Allen weight-drop device that produces 257–722 g-cm of energy on the spinal cord 	<p>In the compression group, pressure was maintained at a constant level for 4–8 weeks until neurologic recovery no longer occurred. If the animal had ceased to recover neurologic function at the 4-week post-operative interval, the transducer was retracted or removed and all subsequent recovery was observed and recorded (4–8 weeks).</p>	<ul style="list-style-type: none"> ◦ Central cord paralysis was noted in seven and anterior cord syndrome in one. ◦ The onset of paralysis was observed within 12–72 h of application of anterior cord pressure. ◦ Significant motor recovery occurred in all eight animals to some degree within 48 h after removing pressure from the spinal cord. ◦ All eight animals were able to walk a plane inclined up to 20°. ◦ Of the eight pressure-induced SCIs that recovered, microscopic examination was normal in two, central gray necrosis occurred in two, peripheral demyelination in two, and lacerations occurred in three. ◦ Time from initial paralysis to recovery of grade 5 ranged from 2 days to 6 weeks. ◦ Pathological findings: mild anterior horn gray matter necrosis in two, laceration of the ventral white and gray matter in three, and no microscopic evidence of cord damage in one, even though significant paralysis occurred. ◦ In general, the cord conduction is abolished with severe injury and if electrical conduction does not return within hours, severe damage has occurred and the animal does not recover neurologic function. ◦ The CEP is also chronologically related to progression of the SCI. ◦ Improvement in neurologic function after injury was reflected by improvement in the CEP response. In this study the CEP response closely paralleled the degree of initial SCI either from contusion or compression as well as the neurologic recovery of the animals.

Dolan et al. (1980)	<ul style="list-style-type: none"> • N = 91 • Rats (white Wistar) • Sex: female • Weight: 280–300 g • Level: T1 	Inclined plane test. Nonlinear regression analysis.	Spinal cord clip compression as developed by Rivlin and Tator (1978).	Laminectomy without SCI (myelotomy group). Ten rats received no anesthetic but had no surgery (control group). The other animals had compression of 16, 71, or 178 g for 3, 30, 60, 300, or 900 sec.	<ul style="list-style-type: none"> • In each group there was very little change in the angle achieved on the inclined plane from week to week. • The overall mean over the 8-week period for the control group was 81.4° and for the myelotomy group was 23°. • Functional recovery decreased as the duration of compression increased. • Functional recovery decreased as the force of compression increased. • Mathematical modeling produced a curve defining the relationship between force, duration, and functional recovery for each week after injury.
Aki and Taya (1984)	<ul style="list-style-type: none"> • N = 33 • Dogs • Level: thoracolumbar 	SEP, blood flow, and histopathological examination. No statistical analysis.	Spinal cord device that delivers compressions at an area of 3.5 × 5 mm with weights of 6, 16, 36, and 60 g.	Spinal cord of dogs was compressed for periods of 30 or 60 min followed by removal of compression.	<ul style="list-style-type: none"> ◦ With increasing compressive weights (6–60 g), SEP amplitudes were progressively more reduced and latencies more prolonged. ◦ Following release of compression, amplitudes and latencies recovered at the lower weights but were more likely to reflect greater conduction deficits with progressively greater weights. ◦ Amplitudes before compression ranged from 3.1 to 36 μV and latencies ranged from 5.0 to 6.5 msec. ◦ Poor arterial and venous filing was observed for 36- and 60-g weights but not for 6- and 16-g weights. ◦ No significant differences between 30 and 60 min of compression were observed with regard to circulatory disturbances. ◦ Pathologic findings: hemorrhage and necrosis were not found in the gray and white matter in the groups weighted with 6 and 16 g, whereas small petchial hemorrhages and tissue necrosis were observed in the center of the gray matter in the groups weighted with 36 and 60 g. ◦ However there were no distinct findings in the white matter with these higher weights.
Guha et al. (1987)	<ul style="list-style-type: none"> • N = 75 • Rats (Wistar) • Sex: female • Weight: 240–280 g • Level: C7–T1 	Inclined plane test. Univariate analysis, multiple comparisons using Student–Newman–Keuls test.	Spinal cord clip compression as developed by Rivlin and Tator (1978).	Animals had clip compression of 2.3, 16.9, or 53 g for 15, 60, 120, or 240 min in a 3 × 4 factorial design study.	<ul style="list-style-type: none"> ◦ The major determinant of recovery was the intensity of compression applied to the spinal cord. ◦ The time until decompression also affected recovery, but only for the lighter compression forces (2.3 and 16.9 g).

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TABLE 1. CONTINUED

References	Sample features	Outcome measures	Injury model	Timing of decompression	Study conclusions
Nystrom and Berglund (1988)	<ul style="list-style-type: none"> • $N = 81$ • Rats (Sprague-Dawley) • Sex: males • Weight: 231–319 g • Level: T7–8 	Inclined plane test. Student's t test.	Thoracic spinal cord compression was created by loading a 2.2×5.0 mm plate with weights of 20, 35, or 50 g.	Three different weights were applied for 1, 5, and 10 min. For ethical reasons 50 g was not paired with 10 min.	<ul style="list-style-type: none"> • The 10-min compression rats were able to fully recover after 20 g compression, but not after 35 or 50 g during the first 21 days after SCI. • At 20 g, the duration of compression did not affect the animals' ability to recover completely. • During the initial 4–5 days, the 1-min compression group differed from the groups subjected to compression for 5 and 10 min ($p < 0.01$). • At 35 g, the 5-min compression group had more severe deterioration than the 1-min group, but animals were able to completely recover. • At 35 g, the 10-min compression group showed the same neurological deterioration as the 5-min compression group during the first 2 days, but the recovery was slower and incomplete in the 10-min group. • At 50 g, 1- and 5-min compression groups showed capacity angle values of about 22°, but recovery was slow and incomplete. Of note, control animals showed a mean capacity angle of $65.2 \pm 0.6^\circ$. • All 30 dogs developed caudal equina syndrome after constriction. • All dogs recovered significant motor function 6 weeks after decompression. • All groups recovered to walking (Tarlov Grade 5) with bladder and tail control at 6 weeks after SCI. • Immediately after compression, all five groups demonstrated $>50\%$ deterioration of the posterior tibial nerve SSEP amplitudes. At 6 weeks after decompression, all five groups had a mean amplitude recovery of 20–30%. There was no difference in recovery of SSEPs among the groups. • All groups demonstrated scattered wallerian degeneration and axonal regeneration. There were no significant differences in the histological findings among the five groups.
Delamarter et al. (1991)	<ul style="list-style-type: none"> • $N = 30$ • Dogs (pure bred beagle hounds) • Sex: females • Weight: 10–12 kg • Level: cauda equina 	Tarlov test, SSEP, and histopathological examination. Paired t test and ANOVA.	The entire caudal equina was constricted circumferentially with a nylon electrical cable, 2.8 mm wide.	Dogs in Group 1 were constricted and immediately decompressed (compression for 2–3 sec). The other groups of dogs had compression times of 1 h, 6 h, 24 h, and 1 week.	<ul style="list-style-type: none"> • In Groups 2 and 3, lactate levels increased 6 to 7 times the basal levels in the first fraction. Group 2 levels normalized within about 30 min, while Group 3 levels were a lot slower in recovering. • Group 4 lactate levels increased 10-fold in the second fraction. Only partial recovery was seen in the 2-h period. • No significant change in pyruvate levels was seen in any of the groups. • Inosine levels rose $0.7\text{--}0.9 \mu\text{M}$ in Groups 2 and 3 and $1.4 \mu\text{M}$ in Group 4. • Inosine recovery was faster than lactate with the Group 4 recovering completely in about 40 min. • Recovery of hypoxanthine was more delayed compared to other metabolites. Complete recovery took almost 80 min.
Zhang et al. (1993)	<ul style="list-style-type: none"> • $N = ?$ • Rats (Sprague-Dawley) • Weight: 350–450 g • Level: T7–8 	Concentration of lactate, inosine, and hypoxanthine, and an increase in the acetate/pyruvate ratio in the extracellular fluid of the gray matter of the dorsal horn. One-way ANOVA and Tukey's test.	Spinal cord compression device that applied 9, 35, or 50 g over exposed spinal cord.	Group 1 included laminectomized animals (control). Group 2 included compression of 9 g for 5 min. Group 3 included compression of 35 g for 5 min. Group 4 had a compression of 50 g for 5 min.	<ul style="list-style-type: none"> • In Groups 2 and 3, lactate levels increased 6 to 7 times the basal levels in the first fraction. Group 2 levels normalized within about 30 min, while Group 3 levels were a lot slower in recovering. • Group 4 lactate levels increased 10-fold in the second fraction. Only partial recovery was seen in the 2-h period. • No significant change in pyruvate levels was seen in any of the groups. • Inosine levels rose $0.7\text{--}0.9 \mu\text{M}$ in Groups 2 and 3 and $1.4 \mu\text{M}$ in Group 4. • Inosine recovery was faster than lactate with the Group 4 recovering completely in about 40 min. • Recovery of hypoxanthine was more delayed compared to other metabolites. Complete recovery took almost 80 min.

Delamarter et al. (1995)	<ul style="list-style-type: none"> • N = 30 • Dogs (pure bred beagle hounds) • Sex: female • Weight: 10–12 kg • Level: L4 	SSEP, Tarlov test, histopathological examination, and electronic microscopy. Paired <i>t</i> test and ANOVA.	The caudal part of the spinal cord and dura were constricted circumferentially with a nylon electrical cable, 2.8 mm wide, to 50% of the diameter of the spinal canal.	Dogs in Group 1 were constricted and immediately decompressed (compression for 2–3 s). The other dogs were compressed for 1 h (Group 2), 6 h (Group 3), 24 h (Group 4), and 1 week (Group 5).	<ul style="list-style-type: none"> • The dogs with immediate decompression generally recovered neurological function within 2–5 days. • They recovered to walking by 1 week and Tarlov Grade 5 with bladder and tail control at 6 weeks after SCI. • Significant SSEP and motor recovery was observed among animals in Groups 1 and 2. • However, animals that were compressed for 6 h or more showed no significant motor recovery after decompression of spinal cord. • SSEP improved an average of 85% in Group 1, 72% in Group 2, 29% in Group 3, 26% in Group 4, and 10% in Group 5 ($p < 0.0008$). • Discrete areas of wallerian degeneration and demyelination were seen in the spinal cord of animals in Groups 1 and 2. In contrast, there was severe central necrosis in the spinal cord of animals that were decompressed at 6 h or later.
Carlson et al. (1997a)	<ul style="list-style-type: none"> • N = 21 • Dogs (beagles) • Weight: 11–14 kg • Level: T13 	SEP, blood flow, and reperfusion flow. ANOVA and paired <i>t</i> tests	Dynamic cord compression was initiated through the loading device pre-calibrated to displace the spinal cord at a constant 0.17 mm/min.	<p>Piston displacement was halted stopping dynamic compression when lower extremity SEP amplitudes were reduced by 50% of baseline (to). At this endpoint spinal cord displacement was maintained for 30 min ($n = 7$), 60 min ($n = 8$), or 180 min ($n = 6$).</p>	<ul style="list-style-type: none"> • SEP recovery was seen in six of seven dogs in the 30-min group, five of eight dogs in the 60-min group, and zero of six dogs in the 180-min compression group. • Recovery in the 30-min and 60-min compression groups was significantly different from the 180-min compression group ($p < 0.05$). • Regional spinal cord blood flow at baseline, 21.4 ± 2.2 mL/100 g/min decreased to 4.1 ± 0.7 mL/100 g/min after stopping dynamic compression. • Reperfusion flows after decompression was inversely related to duration of compression. • Of the dogs in 30-min compression group, 5 min after decompression the blood flow was greater than 2 times baseline. • However, the early post-decompression blood flow was not significantly different from baseline in the 180-min compression group. • Of the eight dogs in the 60-min compression group, five that recovered SEP conduction revealed a lower spinal cord blood flow sampled immediately after stopping dynamic compression, compared to the three that did not recover ($p < 0.05$). • Reperfusion flows measured as the interval change in blood flow between the time dynamic compression was stopped to 5, 15, or 180 min after decompression, were significantly greater in those dogs that recovered SEP ($p < 0.05$). • 3 h after decompression, spinal cord blood flow in the three dogs in the 60-min compression group with no recovery was significantly less than the spinal cord blood flow of the recovered group. • Spinal cord decompression within 1 h of SEP loss resulted in significant electrophysiological recovery after 3 h of monitoring.

(Continued)

TABLE 1. CONTINUED

References	Sample features	Outcome measures	Injury model	Timing of decompression	Study conclusions
Carlson et al. (1997b)	<ul style="list-style-type: none"> • N = 12 • Dogs (beagles) • Weight: 10–12 kg • Level: T13 	SSEP and regional spinal cord blood flow. Paired <i>t</i> test.	Constant velocity spinal cord compression was applied using a hydraulic loading piston with a subminiature pressure transducer rigidly attached to the spinal column. Spinal cord displacement was stopped when SSEP amplitudes decreased by 50% (maximum compression).	Six animals were decompressed 5 min after maximum compression and were compared with six animals that had spinal cord displacement maintained for 3 h and were not decompressed.	<ul style="list-style-type: none"> • At maximum compression, regional spinal cord blood flow at the injury site fell from 19.0 ± 1.3 to 12.6 ± 1.0 mL/100 g/min, whereas piston-spinal cord interface pressure was 30.5 ± 1.8 kPa, and cord displacement measured 2.1 ± 0.1 mm. • 5 min after the piston translation was stopped the spinal cord interface pressure had dissipated 51%, whereas the SSEP amplitudes continued to decrease to 16% of baseline. • In the sustained compression group, cord interface pressure relaxed to 13% of maximum within 90 min. However, no recovery of SSEP occurred and blood flow remained significantly lower than baseline at 30 and 180 min after maximum compression. • In the six animals that underwent spinal cord decompression, SSEP and blood flow recovered to baseline 30 min after maximum compression. • Despite rapid cord relaxation of more than 50% within 5 min after maximum compression, SSEP recovered with early decompression. • Spinal cord decompression was associated with an early recovery of blood flow and SSEP recovery. • By 3 h, blood flow was similar in both the compressed and decompressed groups, even though SSEP recovery occurred only in the decompressed group.
Dimar et al. (1999)	<ul style="list-style-type: none"> • N = 42 • Rats (Sprague Dawley) • Age: 12 weeks • Weight: 298.7 g • Level: T9 	tcMMEPs, BBB, and histopathological examination. Wilcoxon signed rank test, and ANCOVA.	A 12.5-g-cm spinal cord contusion was produced using an impactor (developed at New York University).	Rats were divided into five groups based on duration of spinal cord compression: 0 (the spacer was placed into the canal and immediately removed), 2, 6, 24, and 72 h.	<ul style="list-style-type: none"> • Shorter duration of spacer placement was associated with greater BBB scores over the 6-week recovery period ($p < 0.05$). • Statistical difference was found in the tcMMEPs response rates in the groups with 0-h and 2-h compression in comparison with the other groups ($p < 0.05$). There were no significant differences among the 6-, 24-, and 72-hour groups. • There was a progressively more severe central and dorsal cavitation as the time of spinal cord compression increased. • Midsagittal sections demonstrated progressive cephalad and caudal cord necrosis and cavitation, which worsened the longer the duration of compression. These changes were most severe in the 24- and 72-h specimens.

Carlson et al. (2003)	<ul style="list-style-type: none"> • $N = 16$ • Dogs (beagles) • Weight: 11–15 kg • Level: T13 	<p>SSEP, Tarlov motor test, balance test, stair-climbing test, inclined-plane test, and lesion volume (examined using MRI and histology). ANOVA, Mann–Whitney rank sum test, Friedman repeated measures ANOVA.</p>	<p>The spinal cord was compressed using a loading device with a hydraulic piston. A dynamic compression with a loading device precalibrated at a constant 0.17 mm/min.</p>	<p>When SSEP declined by 50%, dynamic compression was no longer increased but was sustained for 30 min in 8 dogs and for 180 min in 8 dogs. After designated time, the compression was discontinued.</p>	<ul style="list-style-type: none"> • After decompression, SSEP returned in all dogs in the 30-min compression group, with recovery to 63% of the baseline value at 90 min after decompression. • At 28 days after the injury, the mean amplitude of the SSEP was 38% of the baseline in the 30-min compression group. • In contrast, in the 180-min compression group, decompression did not result in recovery of SSEP either early or late. • The mean modified Tarlov motor scores were significantly better for the 30-min compression group than for the 180-min compression group at all time points. • At 2 weeks after SCI the 30-min compression group did better than the 180-min compression group in balance ($p < 0.01$), cadence ($p < 0.001$), stair climbing ($p < 0.01$), and ability to walk up an inclined plane. • Lesion volumes as assessed using MRI were smaller in the 30-min compression group than the 180-min compression group ($p = 0.04$). • The 30-min compression group showed smaller lesion volume ($p < 0.001$) and greater percentage of residual white matter ($p = 0.005$) than the 180-min compression group.
Hejcl et al. (2008)	<ul style="list-style-type: none"> • $N = 23$ • Rats (Wistar) • Weight: 300–350 g • Age: 8 weeks • Sex: male • Level: T9 	<p>BBB scores, MRI, histopathological examination. Student's unpaired t test</p>	<p>Spinal cord transection</p>	<p>In 10 animals the dura was only sutured (Control). In seven animals a block of HEMA-MOETACI hydrogel was inserted right away after SCI (acute group). In six animals the block of hydrogel was implanted 1 week after SCI (delayed group).</p>	<ul style="list-style-type: none"> • Both the early and delayed implantation group showed good hydrogel integration inside the lesion. • The control group differed significantly in the volume of pseudocyst compared to the acute ($p < 0.001$) and delayed ($p < 0.05$). • There was no significant difference in histopathological examination of spinal cord between the acute and delayed implantation groups. • There were no significant differences between the two treatment groups with regard to the BBB scores.

(Continued)

TABLE 1. CONTINUED

References	Sample features	Outcome measures	Injury model	Timing of decompression	Study conclusions
Rabinowitz et al. (2008)	<ul style="list-style-type: none"> • N = 18 • Dogs (beagle) • Adult (10–12 kg) • Sex: male • Level: L4 (thoracolumbar junction) 	<p>Modified Tarlov grading system, SSEPs, histopathology, exact</p> <p>Wilcoxon's rank sum tests—ordinal variables, Fisher exact test—nominal variables, Kruskal-Wallis tests—difference in medians for continuous non-Gaussian variables, Bonferroni adjustment for multiple comparisons.</p>	<p>Dura at the thoracolumbar junction was constricted circumferentially with a nylon band, 2.8 mm wide, to 60% of the diameter of the spinal canal.</p>	<p>Group 1: decompression at 6 h + methylprednisolone; Group 2: decompression at 6 h + sham; Group 3: methylprednisolone only.</p>	<ul style="list-style-type: none"> ◦ All animals were paraplegic (Tarlov Grade 1) after spinal cord compression. ◦ All animals lost SSEPs after spinal cord compression. ◦ Decompression within 6 h (Groups 1 and 2) showed significant neurological improvement when compared to no decompression (Group 3). ◦ Methylprednisolone did not significantly affect outcome. ◦ Groups 1 and 2 regained SSEPs at 2 weeks to 69% and 52%, respectively; in Group 3 only one animal regained SSEPs to 25%. ◦ None of these comparisons were statistically significant. ◦ There was no statistical difference in the percentage of cord involvement histologically between the three groups; Group 3 showed greater involvement below the level of the lesion.

SCI, spinal cord injury; CEP, cortical evoked potentials; SSEP, somatosensory evoked potentials; CER, cortical evoked response; SEP, spinal-evoked potentials; tcMMEPs, transcranial magnetic motor evoked potentials; ANOVA, Analysis of Variance; ANCOVA, Analysis of covariance; BBB, Basso, Beattie, Bresnahan Locomotor Rating Scale; MRI, magnetic resonance imaging; SER, spinal evoked response.

TABLE 2. SUMMARY OF THE CLINICAL STUDIES ON TIMING OF SURGICAL DECOMPRESSION OF SPINAL CORD FOR PATIENTS WITH TRAUMATIC SPINAL CORD INJURY

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
Levi et al. (1991)	Patients admitted with middle to lower cervical spine trauma during July 1985 through June 1990 who underwent anterior cervical decompression and stabilization were included.	<ul style="list-style-type: none"> • N (all cases) = 103 • Incomplete deficit, early surgery: <ul style="list-style-type: none"> ◦ N = 35 ◦ Median age: 30.4 years • Males: 80% • Incomplete deficit, delayed surgery: <ul style="list-style-type: none"> ◦ N = 18 ◦ Median age: 33 years ◦ M: 80% • Complete deficit, early surgery: <ul style="list-style-type: none"> ◦ N = 10 ◦ Median age: 24.9 years • Males: 85.7% • Complete deficit, delayed surgery: <ul style="list-style-type: none"> ◦ N = 40 ◦ Median age: 27.6 years ◦ Males: 83.3% 	<ul style="list-style-type: none"> ◦ Level of injury: <ul style="list-style-type: none"> ◦ C3: 9 ◦ C4: 11 ◦ C5: 48 ◦ C6: 25 ◦ C7: 10 ◦ Cause of SCI: <ul style="list-style-type: none"> ◦ MVA: 55 ◦ Diving: 24 ◦ Fall: 15 ◦ Other: 9 ◦ Associated traumatic brain injury (GCS < 14): <ul style="list-style-type: none"> ◦ Incomplete deficit group: 10% ◦ Complete deficit group: 7.5% 	<ul style="list-style-type: none"> • Early surgery group: ≤24 h • Delayed surgery group: >24 h 	Hospital LOS, complications, respiratory care, neurological assessment using Yale motor score, and functional assessment using the modified Frankel score of Benzel and Larson	<ul style="list-style-type: none"> • In the incomplete deficits group (Group A) one patient in the delayed surgery group died. • There was a significant difference in the hospital LOS between the early and delayed surgery groups (38.7 vs. 45.2 days; $p < 0.05$). • Respiratory care was significantly more required in the early surgery group than the delayed surgery group ($p < 0.05$). • There were no significant differences between early and delayed surgery groups with regard to the frequency of complications ($p > 0.05$). • In the complete deficits group (Group B), one patient died in the early surgery group. • All patients with a deficit progressed to a higher functional grade. • Early surgery group was not significantly different from delayed surgery group regarding neurological and functional recovery (no p value was reported). 	4	10

(Continued)

TABLE 2. CONTINUED

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
Clohisy et al. (1992)	Patients with incomplete neurological deficits after thoracolumbar injury who underwent spinal canal decompression and stabilization from 1981 to 1990 were included.	<ul style="list-style-type: none"> • N = 20 • Mean age: 33 years (15–66 years) • Males/females: 12/8 	<p>Level of injury:</p> <ul style="list-style-type: none"> ◦ T12: 9 ◦ L1: 11 <p>Type of SCI:</p> <ul style="list-style-type: none"> ◦ Unstable burst fracture: 14 ◦ Fracture dislocation: 6 <p>Severity of SCI (modified Frankel scale):</p> <ul style="list-style-type: none"> ◦ A: 1 ◦ B: 2 ◦ C: 8 ◦ D: 9 	<ul style="list-style-type: none"> • Group A: anterior decompression ≤48 h • Group B: anterior decompression >48 h 	<ul style="list-style-type: none"> • Neurologic recovery as assessed by the modified Frankel scale and ASIA motor score. • Conus medullaris recovery based on the frequency of lack of bladder and bowel control and perianal anesthesia. 	<ul style="list-style-type: none"> • Although four patients had neurological deterioration prior to surgery (three in Group A; one in Group B), no patients had any deterioration in neurologic function after surgery. • Group A had significant mean modified Frankel grade improvement when compared to Group B ($p < 0.04$). • The mean ASIA motor score improvement among patients in Group A was greater than the motor improvement among patients in Group B ($p = 0.01$). • While four of nine patients in Group A completely recovered from a conus medullaris syndrome, six of nine patients in Group B partially recovered ($p = 0.1$). 	4	13
Krengel et al. (1993)	<ul style="list-style-type: none"> • Patients with incomplete paraplegia due to acute SCI between T2 and T11 admitted from 1985 to 1990 were included. • Patients with complete SCI or conus medullaris lesions were excluded. 	<ul style="list-style-type: none"> • N (all cases) = 14 • N (early surgery group) = 12 • N (late surgery group) = 2 • Mean age: 35 years (14–75 years) • Males: 14 	<p>Level of injury:</p> <ul style="list-style-type: none"> ◦ T3–T7: 10 ◦ T10–T11: 4 <p>Mean follow-up time: 20 months (12–65 months)</p> <p>Cause of SCI:</p> <ul style="list-style-type: none"> ◦ MVA: 6 ◦ Fall: 6 ◦ Crushing: 2 <p>Type of injury:</p> <ul style="list-style-type: none"> ◦ Burst fracture: 4 ◦ Fracture dislocation: 12 	<ul style="list-style-type: none"> • Early surgery group: ≤24 h • Late surgery group: >24 h 	<p>Neurologic improvement of at least one Frankel grade, and surgical complications.</p>	<ul style="list-style-type: none"> • All 12 patients who underwent early surgery recovered at least one Frankel grade. • No patient showed neurological deterioration after surgery. • There were no wound infections or pseudoarthrosis. • One patient had his rod removed earlier because the hook dislodged. 	4	7

Duh et al. (1994)	<ul style="list-style-type: none"> Patients admitted with acute SCI from May 1985 to December 1988 were included. Patients with spinal nerve root damage only, cauda equina lesions only, injury by gunshot, other serious comorbidity, pregnancy, use of maintenance corticosteroids for other reasons, narcotic addiction, and age <13 years were excluded. 	<ul style="list-style-type: none"> N = 487 	<p>Not reported in the paper. However, this information is available in the original publication of the Second National Spinal Cord Injury Study (NASCIS-II) in JAMA (1990): sex, age, ethnic group, height, weight, blood pressure on admission, cause of injury, associated injuries, GCS, severity of injury and cord syndrome.</p>	<ul style="list-style-type: none"> Early surgery group: ≤ 25 h Intermediate surgery group: from 26 to 200 h Late surgery group: >200 h 	<ul style="list-style-type: none"> Neurological improvement of at least 5 points in the NASCIS-II motor score. NASCIS-II motor score 	<ul style="list-style-type: none"> The results suggest that either early surgery or late surgery may be associated with increased neurological recovery, particularly motor function, but these results were equivocal. Logistic regression analysis adjusted for severity of SCI indicated that the timing of surgery as assessed by the three study groups was not significantly associated with neurological improvement of at least 5 points in the NASCIS-II motor scores from baseline to 6 weeks ($p > 0.31$), 6 months ($p > 0.7$), or 1 year following SCI ($p > 0.67$). Early surgery group and intermediate/late surgery group (>25 h) did not differ regarding the improvement in the NASCIS-II motor score at 6 weeks ($p = 0.43$), at 6 months ($p = 0.16$), or at 1 year after SCI ($p = 0.14$) after adjusting for age and severity of SCI. 	4	18
Botel et al. (1997)	<ul style="list-style-type: none"> All patients admitted from January 1, 1993, to December 31, 1995, with SCI were included. 	<ul style="list-style-type: none"> N (all cases) = 255 N (traumatic SCI) = 205 Mean age: 39.3 years (2–82 years) Males/females: 72%/28% 	<p>Level of SCI:</p> <ul style="list-style-type: none"> Tetraplegia: 31.4% Paraplegia: 68.6% 	<p>Early surgery: ≤ 24 h</p>	<p>Feasibility of early operation.</p>	<ul style="list-style-type: none"> 42.2% of patients reached the hospital within the first 24 h. Of these 64.4% were admitted within the first 8 h of SCI. Of the remaining 23.6% cases from other centers, 45.2% had to undergo corrective re-operations. 178 of 255 patients required spine surgery. Of those 178 patients, 92 (51.4%) could be stabilized within 24 h after SCI. "The time of operation depended on the day of admission on the one hand but on the state of the patient at the other, especially regarding patients with severe polytrauma and thoracic injuries." 	4	11

(Continued)

TABLE 2. CONTINUED

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
Campagnolo et al. (1997)	<ul style="list-style-type: none"> All patients with traumatic SCI included in the Northern New Jersey Spinal Cord Injury System Database between 1990 and 1996. 	<p>Early surgery group:</p> <ul style="list-style-type: none"> N = 37 Mean age: 32.4 years Males/females: 35/2 <p>Late surgery group:</p> <ul style="list-style-type: none"> N = 27 Mean age: 41.9 years Males/females: 23/4 	<p>Early surgery group:</p> <ul style="list-style-type: none"> Paraplegic complete: 7 Paraplegic incomplete: 7 Tetraplegics complete: 12 Tetraplegics incomplete: 11 <p>Late surgery group:</p> <ul style="list-style-type: none"> Paraplegic complete: 8 Paraplegic incomplete: 4 Tetraplegics complete: 8 Tetraplegics incomplete: 7 	<ul style="list-style-type: none"> Early spinal stabilization group: ≤ 24 h Late spinal stabilization group: > 24 h 	LOS in the acute SCI care, ISS, and frequency of complications in the acute stage after SCI.	<ul style="list-style-type: none"> Mean LOS in the early surgery group (37.5 days) was smaller than in the late surgery group (54.7 days; $p = 0.01$). The early surgery group did not differ from the late surgery group regarding the mean ISS (17.9 vs. 21.3, respectively; $p = 0.10$). Both groups did not differ regarding the frequency for need for mechanical ventilation ($p = 0.66$), decubitus ulcers ($p = 0.33$), atelectasis/pneumonia ($p = 0.56$), wound infections ($p = 0.63$), autonomic dysreflexia ($p = 0.64$), DVT ($p = 0.64$), cardiac arrest ($p = 1$), urinary calculus ($p = 0.43$), gastrointestinal hemorrhage ($p = 0.43$), spasticity ($p = 0.43$), heterotopic ossification ($p = 0.56$), or UTI ($p = 0.99$). 	4	12
Vaccaro et al. (1997)	<p>The inclusion criteria were (1) patients with SCI at C3–T1, and age from 15 to 75 years; (2) patients admitted within 48 h of SCI; (3) spinal cord compression in an imaging study. The exclusion criteria were (1) associated injuries that precluded the neurologic examination or surgery; (2) pre-existing comorbidities that interfered in the neurological examination or surgery.</p>	<p>N (all cases) = 62</p> <p>Early surgery group:</p> <ul style="list-style-type: none"> N = 34 Mean age: 39.79 years Males/females: 24/10 <p>Late surgery group:</p> <ul style="list-style-type: none"> N = 28 Mean age: 39 years Males/females: 22/6 	Level of injury: C3–T1	<ul style="list-style-type: none"> Early surgery group: ≤ 72 h Late surgery group: > 5 days 	Hospital LOS, length of rehabilitation, improvement of AIS.	No significant differences were seen in LOS in the acute post-operative ICU, length of inpatient rehabilitation or improvement in AIS, or ASIA motor score between the early vs. late surgery groups (no p values were reported).	2b	12

McLain and Benson (1999)	<ul style="list-style-type: none"> • Patients admitted from January 1988 to December 1993 who underwent posterior spinal stabilization were included. 	<ul style="list-style-type: none"> • <i>N</i> (all cases) = 27 • Males/females: 21/6 • <i>N</i> (urgent surgery group) = 14 • <i>N</i> (early surgery group) = 13 • Mean age (urgent surgery group): 27.5 years (16–46 years) • Mean age (early surgery group): 30 years (18–58 years) 	<p>Level of injury:</p> <ul style="list-style-type: none"> ◦ Thoracic: 9 ◦ Lumbar: 18 <p>Etiology of injury:</p> <ul style="list-style-type: none"> ◦ MVA: 74% ◦ Fall: 18.5% ◦ Crushed by collapsing walls: 7.5% 	<ul style="list-style-type: none"> • Urgent surgery group: ≤24h • Early surgery group: from 24 to 72h 	Neurological assessment (Frankel grade improvement, frequency of patients with neurological improvement, back pain score), change, mortality, medical complications and frequency of return to work.	<ul style="list-style-type: none"> • The mean ISS was 36 for early surgery group and 42 for urgent surgery group (no <i>p</i> was reported). • One patient died in each group. • Urgent group showed a higher mean neural improvement (1.12 vs. 0.65) and proportion with neurological improvement (88% vs. 50%) than early group (no <i>p</i> was reported). • Blood loss for anterior procedures was significantly higher in the urgent group but estimated blood loss for posterior procedures was similar for both groups (no <i>p</i> was reported). • At 49 months follow-up time, no revisions were necessitated by the urgent spinal treatment. 	4	10
Mirza et al. (1999)	<ul style="list-style-type: none"> • Patients included were those with acute traumatic cervical SCI, ISS < 30, indirect neurologic decompression by immediate closed reduction, and surgical management of cervical spinal injury who were admitted from March 1989 to May 1991. • Patients with severe closed head injury and an ISS ≥ 30 were excluded. 	<ul style="list-style-type: none"> • <i>N</i> (all cases) = 30 • <i>N</i> (early surgery group) = 15 • <i>N</i> (late surgery group) = 15 • Age range: 14–56 years • Males/females: 26/4 	<p>Level of injury: C2–C7</p> <p>Injury severity:</p> <ul style="list-style-type: none"> ◦ ISS (early surgery group): 24.8 ◦ ISS (late surgery group): 26.2 <p>Cause of injury:</p> <ul style="list-style-type: none"> ◦ MVA: 19 ◦ Fall: 3 ◦ Diving: 5 ◦ Assault: 3 <p>Type of spine injury:</p> <ul style="list-style-type: none"> ◦ Burst fracture: 10 ◦ Dislocation: 16 ◦ Subluxation: 2 ◦ Extension injury: 1 ◦ Herniated disc: 1 	<ul style="list-style-type: none"> • Early surgery group: ≤72h • Late surgery group: >72h 	Neurological assessment (ASIA motor index and Frankel grade), hospital LOS, and frequency of acute complications.	<ul style="list-style-type: none"> • The duration of acute LOS was longer in the late surgery group than the early surgery group (36.8 vs. 21.9 days; <i>p</i> = 0.04). • The post-operative motor index scores were significantly different for the two groups (<i>p</i> = 0.01). • The change in the motor score from preoperative assessment to post-operative assessment was significant in the early surgery group (<i>p</i> = 0.006) but not in the late surgery group (<i>p</i> = 0.14). • While early surgery group showed significant improvement in the Frankel grade after surgery (<i>p</i> = 0.003), there was no significant differences between preoperative and post-operative assessments using Frankel grade in the late surgery group (<i>p</i> = 0.3). • The number of total complications was significantly greater in the late surgery group than the early surgery group (<i>p</i> = 0.05). 	4	10

TABLE 2. CONTINUED

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
Ng et al. (1999)	<ul style="list-style-type: none"> Patients with cervical (C3–T1) SCI eligible for a decompressive therapy within 8 h of injury who were admitted in one of the participating centers from October 1996 to January 1997 were included. 	<ul style="list-style-type: none"> N = 26 Mean age: 30.3 years (18–68 years) Males/females: 22/4 	Cause of injury: <ul style="list-style-type: none"> MVA: 58% Fall: 15% Sports: 6% Assault: 4% AIS: <ul style="list-style-type: none"> A: 13 B: 4 C: 2 D: 7 	<ul style="list-style-type: none"> Early surgery group: ≤8 h Late surgery group: >8 h 	Change in AIS, time required for imaging, and decompressive surgery.	<ul style="list-style-type: none"> Decompression by traction required an average of 10.9 h. Only 6 out of the 11 were able to get the procedure within 8 h of injury. Only two patients underwent a surgical decompressive procedure within 8 h post-injury. After surgery 84.6% of patients remained as ASIA grade A. 19.2% improved from grade D to E in 6 months and had an average time of decompressive treatment of 30.8 h post-injury. One patient died of sepsis and pneumonia. 	4	11
Tator et al. (1999)	<ul style="list-style-type: none"> Patients with SCI or cauda equina injuries admitted from August 1994 to April 1995, within 24 h of injury were included. Subjects with gunshot wound or without signs of compression in imaging studies were excluded. 	<ul style="list-style-type: none"> N = 585 Mean age: 40 years 	Level of injury: <ul style="list-style-type: none"> C1–7: 64.6% T1–11: 18.7% T11–L2: 11% L2–S5: 5.6% Severity of injury (AIS): <ul style="list-style-type: none"> A: 42.2% B: 9.7% C: 22.4% D: 25.5% 	<ul style="list-style-type: none"> Surgery ≤24 h Surgery between 25 and 48 h Surgery between 48 and 96 h Surgery >5 days 	Feasibility of early operation.	<ul style="list-style-type: none"> The timing of surgery varied: less than 24 h post-injury in 23.5%, between 25 and 48 h post-injury in 15.8%, between 48 and 96 h in 19%, and more than 5 days post-injury in 41.7% of patients. 	4	9
Guest et al. (2002)	<ul style="list-style-type: none"> Only patients with central cord syndrome admitted between 1986 and 1996 were included. 	<ul style="list-style-type: none"> N = 50 Mean age: 45 years (14–77 years) Males/females: 31/19 	Cause of injury: <ul style="list-style-type: none"> MVA: 22 Fall: 19 Sports: 9 Mean follow-up time: 36 months (13–48 months).	<ul style="list-style-type: none"> Early surgery group: ≤24 h Late surgery group: >24 h 	<ul style="list-style-type: none"> Post-spinal injury motor function scale (PSIMFS) ASIA motor score Bladder function ICU LOS 	<ul style="list-style-type: none"> Both groups were statistically comparable with regard to the PSIMFS ($p = 0.3$), mean admission ASIA motor score ($p = 0.45$), and mean follow-up ASIA motor score ($p = 0.23$). 	4	9

TABLE 2. CONTINUED

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
Papadopoulos et al. (2002)	<ul style="list-style-type: none"> • Patients with acute traumatic closed cervical (C1–T1) SCI admitted from 1990 to 1997 were included. • Patients who received their definitive surgical treatment outside the institution were excluded. 	<ul style="list-style-type: none"> • N (all cases) = 91 • Protocol group: N = 66 • Mean age: 32 years (2–92 years) • Males: 68% • Reference group: N = 25 • Mean age: 42 years (9–75 years) • Males: 76% 	<ul style="list-style-type: none"> • Level of injury: C2–C8, T1 • Time from SCI to operative decompression (protocol group): 12.6 ± 1.3 h 	<ul style="list-style-type: none"> • Protocol group: patients who followed the University of Michigan Acute SCI Protocol, which recommends early surgical decompression of spinal cord. • Reference group: patients not included in the above group due to contraindication to MRI, need for other emergency procedures, or admitting surgeon preference. 	<ul style="list-style-type: none"> • Frankel grade, LOS in the ICU, mortality, general care unit and rehabilitation care unit. 	<ul style="list-style-type: none"> • In patients with ISS <25, patients in the early surgery group had fewer ventilator days ($p < 0.02$), shorter ICU LOS ($p < 0.001$) and hospital LOS ($p < 0.001$), and lower hospital charges ($p < 0.001$) than the late surgery group. • In patients with significant pulmonary injury, patients in the early surgery group had shorter ICU LOS ($p < 0.003$) and hospital LOS ($p < 0.02$), lower hospital charges ($p < 0.02$), and less frequency of pneumonia ($p < 0.003$). • The frequency of DVT was lower in the early group ($p < 0.04$). • There were eight deaths in the early fixation group and four in the late fixation group ($p > 0.05$). • Patients treated using the protocol showed a significantly greater neurological improvement than patients in the reference group ($p < 0.006$). • Using a multiple regression analysis, early spinal cord decompression was significantly correlated with change in Frankel grade from admission to the latest follow-up assessment ($p = 0.048$). • There were no significant differences between both groups regarding in-hospital mortality ($p > 0.05$). 	4	10

Pollard and Apple (2003)	<ul style="list-style-type: none"> Patients with traumatic incomplete cervical SCI admitted within 90 days of injury who completed a full rehabilitation program were included. Patients with confounding physical and neurologic conditions were excluded. 	<ul style="list-style-type: none"> $N = 412$ 	Not reported	<ul style="list-style-type: none"> Early surgery group: ≤ 24 h Late surgery group: > 24 h 	Change in motor score and sensory follow-up motor and sensory scores (ASIA Standards).	<ul style="list-style-type: none"> Neither group significantly differed with regard to change in the ASIA motor score ($p = 0.42$), follow-up ASIA motor scores ($p = 0.73$), change in the ASIA sensory score ($p = 0.49$), and follow-up ASIA sensory score ($p = 0.5$). 	4	11
Chipman et al. (2004)	<ul style="list-style-type: none"> Patients with thoracolumbar spinal column injury registered at the North Memorial Medical Center from January 1994 to July 2001 were included. 	Early surgery and low ISS (< 15): <ul style="list-style-type: none"> $N = 32$ Mean age: 34.3 years Males: 84.4% Mean ISS: 10 Late surgery and low ISS: <ul style="list-style-type: none"> $N = 26$ Mean age: 46.2 years Males: 65.4% Mean ISS: 10.6 Early surgery and high ISS (≥ 15): <ul style="list-style-type: none"> $N = 37$ Mean age: 29.9 years Males: 64.9% Mean ISS: 25.8 Late surgery and high ISS: <ul style="list-style-type: none"> $N = 51$ Mean age: 35.7 years Males: 66.7% Mean ISS: 29.1 	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> Group 1: surgery before 72 h and low ISS (< 15). Group 2: surgery after 72 h and low ISS. Group 3: surgery before 72 h and high ISS (≥ 15). Group 4: surgery before 72 h and high ISS. 	<ul style="list-style-type: none"> Hospital LOS, LOS in the ICU, frequency of infectious complications and respiratory failure. 	<ul style="list-style-type: none"> Although Groups 1 and 2 were comparable with regard to ISS, Group 1 showed lower frequency of anterior fusion ($p = 0.047$) and younger age at the time of injury ($p = 0.01$). There was a trend for a higher proportion of males in Group 1 than in Group 2 ($p = 0.09$). There were no significant differences between Groups 3 and 4 regarding ISS ($p = 0.12$), proportion of males ($p = 0.86$), and frequency of anterior fusion ($p = 0.97$). There was a trend towards a younger age in Group 3 compared to Group 4 ($p = 0.08$). No differences were seen between Groups 1 and 2 with regard to the frequency of infectious complications ($p = 0.44$), respiratory failure ($p = 0.83$), and all complications ($p = 0.59$) and well as the LOS in the ICU ($p = 0.14$). Patients in Group 2 stayed significantly longer in the hospital than patients in Group 1 ($p < 0.001$). 	4	15

TABLE 2. CONTINUED

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
McKinley et al. (2004)	<ul style="list-style-type: none"> Patients admitted within the first 24 h of injury with acute, nonpenetrating, traumatic SCI were included. Patients with penetrating injuries were excluded from analysis because of the potential for spinal cord transection and subsequent diminished potential for neurologic recovery. 	<ul style="list-style-type: none"> N (all cases) = 779 N (early surgery group) = 307 N (late surgery group) = 296 N (non-surgery group) = 176 Mean age: 37.65 years Males/females: 78.8%/21.2% 	<ul style="list-style-type: none"> Level and severity of injury: <ul style="list-style-type: none"> Paraplegia, incomplete: 17.8% Paraplegia, complete: 27.2% Tetraplegia, incomplete: 32.9% Tetraplegia, complete: 22.1% Cause of injury: <ul style="list-style-type: none"> MVC: 52.9% Fall: 28.2% Sports: 9.1% Medical/surgical complication: 2.8% Other violence: 1%; Other cause: 5.9% 	<ul style="list-style-type: none"> Early surgery group (≤ 72 h after SCI), late surgery group (> 72 h) and non-surgery group. In addition, patients who underwent spine surgery was classified into: surgery on day of injury (Group 1): ≤ 24 h after SCI; surgery on day 1 (Group 1.A): < 48 h after SCI; and surgery on day 2 (Group 2): from 24 to 72 h of injury. 	ASIA motor index, ASIA motor index efficiency, neurological level, sensory level, motor level and AIS; frequency of medical complications; hospital LOS; hospital costs; FIM motor change and FIM motor efficiency.	<ul style="list-style-type: none"> While Groups 3 and 4 did not differ regarding the frequency of infectious complications ($p = 0.11$) and respiratory failure ($p = 0.6$), patients in Group 3 showed significantly lower frequency of all complications ($p = 0.03$), shorter hospital LOS ($p < 0.001$), and shorter LOS in the ICU ($p = 0.003$) than patients in Group 4. Groups 3 and 4 were statistically comparable regarding the lowest systolic blood pressure ($p = 0.42$), resuscitation volume in crystalloid ($p = 0.68$), total resuscitation volume ($p = 0.91$), volume of packed red blood cells ($p = 0.24$), volume of platelets ($p = 0.26$), and volume of other colloids ($p = 0.64$). However, Group 4 received a greater volume of fresh frozen plasma than in Group 3 ($p = 0.055$). All three groups were comparable regarding the FIM motor efficiency ($p = 0.38$); FIM motor change from admission to follow-up ($p = 0.81$) and from discharge to follow-up ($p = 0.99$). Patients without spinal surgeries or early spine surgery had shorter acute care and total LOS than those with later surgery ($p < 0.01$). There were no differences among groups regarding the LOS in rehabilitation ($p = 0.31$). 	4	18

- Patients receiving no spinal surgeries or early spine surgery had lower hospital costs in the acute care ($p < 0.01$) and in the rehabilitation ($p = 0.055$) than patients who underwent late surgery.
- The ASIA motor index did not differ among the three groups from acute care admission to rehabilitation ($p = 0.87$), from rehabilitation admission to discharge ($p = 0.42$), and from discharge to follow-up ($p = 0.21$).
- No significant differences between groups were found for changes in neurologic, motor, or sensory levels or AIS grade ($p > 0.15$).
- Late surgery group had higher incidence of pneumonia and atelectasis in acute care ($p = 0.004$), but not in the rehabilitation ($p = 0.62$).
- The frequencies of DVT, pulmonary embolism, autonomic dysreflexia, and pressure ulcers were similar among the three groups in both settings ($p > 0.11$).
- However, the occurrence of autonomic dysreflexia at 1 year after SCI was higher in the late surgery group ($p = 0.03$).
- The groups were comparable regarding rehospitalizations ($p = 0.82$) or rehospitalization days ($p = 0.13$).

(Continued)

TABLE 2. CONTINUED

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
Kerwin et al. (2005)	<ul style="list-style-type: none"> Patients with spine fractures requiring surgical stabilization from January 1988 to October 2001 were included. 	<ul style="list-style-type: none"> N (all cases) = 299 N (early surgery group) = 174 N (late surgery group) = 125 Males/females: 217/82 	<p>Level of injury:</p> <ul style="list-style-type: none"> Cervical: 150 Thoracic: 90 Lumbar: 68 Multiple levels: 9 <p>Cause of injury:</p> <ul style="list-style-type: none"> MVA: 53% Fall: 25% Motorcycle crash: 7% Pedestrian versus vehicle crash: 4% Other cause: 11% 	<ul style="list-style-type: none"> Early surgery group: ≤ 3 days of injury Late surgery group: > 3 days 	Hospital LOS, ICU LOS, time on mechanical ventilation, frequency of pneumonia, modified FIM score, and mortality.	<ul style="list-style-type: none"> Both groups were comparable regarding mean age, GCS, or ISS ($p > 0.05$). The mortality was higher in the early group compared to the late group (6.9% vs. 2.5%), however not statistically significant ($p > 0.05$). The hospital LOS was significantly shorter ($p = 0.0005$) for patients with early spine fixation, but no significant difference between the two groups with regard to ICU LOS ($p > 0.05$), frequency of pneumonia ($p > 0.05$), or number of days in mechanical ventilator ($p > 0.05$). Both study groups were statistically comparable with regard to feeding, motor, and independence components of the modified FIM scores ($p > 0.05$). 	4	12
Schinkel et al. (2006)	<ul style="list-style-type: none"> Patients with thoracic spine injuries with an Abbreviated Injury Scale > 2 were included. 	<p>N (all cases) = 298</p> <p>Early surgery group:</p> <ul style="list-style-type: none"> N = 156 Mean age: 36.7 years Median age: 28 years Mean ISS: 28.5 Mean GCS: 9.7 <p>Late surgery group:</p> <ul style="list-style-type: none"> N = 49 Mean age: 38.1 years Median age: 34 years Mean ISS: 30.9 Mean GCS: 9.1 	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> Group I (early surgery group): ≤ 72 h Group II (late surgery group): > 72 h Group III (control group): no surgery 	<p>Mortality using Trauma Injury-Injury Severity Score (TRISS) method, LOS in the ICU, dependence on mechanical ventilation, ISS and medical complications.</p>	<ul style="list-style-type: none"> Groups II and I were statistically comparable regarding the PaO₂/FiO₂ ratio (Horowitz ratio) ($p > 0.05$), frequency of sepsis ($p > 0.05$), and mortality by TRISS ($p > 0.05$). However, the mortality rate in Group II was significantly higher than in Group I ($p < 0.05$). Patients in Group I had significantly shorter ICU LOS ($p = 0.001$), dependence on mechanical ventilation ($p = 0.02$), and hospital LOS ($p = 0.048$) than Group II. 	4	12

Control group:									
		<ul style="list-style-type: none">◦ N = 93◦ Mean age: 31.7 years◦ Mean ISS: 28.4◦ Mean GCS: 8.4							
Sapkas and Papadakis (2007)	<ul style="list-style-type: none">• Patients with lower cervical spine injury (C3–C7) who were admitted from January 1987 to December 200 were included.	<ul style="list-style-type: none">• N = 67• Mean age: 36 years (16–72 years)• Males/females: 49/18	Severity of SCI: <ul style="list-style-type: none">◦ A: 20◦ B: 10◦ C: 11◦ D: 17◦ E: 9 Causes of SCI: <ul style="list-style-type: none">◦ MVA: 73%◦ Fall: 18%◦ Diving: 7.5%◦ Sports: 1.5% Type of spine injury: <ul style="list-style-type: none">burst fracture (n = 29) or fracture-dislocation (n = 38)	<ul style="list-style-type: none">• Early surgery group: ≤72 h• Delayed surgery group: >72 h	Frankel grade and frequency of medical complications	<ul style="list-style-type: none">• Patients with preoperative Frankel grade A did not improve in neurological status.• Both groups were comparable regarding the neurological improvement among patients with incomplete SCI (<i>p</i> = 0.44)• Two patients with grade-A injury died within 2–4 months of surgery.	4	8	
Cengiz et al. (2008)	<ul style="list-style-type: none">• Patients with acute thoracolumbar SCI at T8–L2 were included.• Patients who were admitted on Monday and underwent an immediate stabilization within 8 h (early surgery), and patients who were admitted on Friday and underwent operation in 3–15 days (late surgery)	<ul style="list-style-type: none">• N (all cases) = 27• Mean age: 41.4 years (23–68 years)• Males/females = 18/9 Early surgery group: <ul style="list-style-type: none">◦ N = 12◦ Mean age: 39.7 years◦ Males/females: 8/4 Late Surgery Group: <ul style="list-style-type: none">◦ N = 15◦ Mean age: 41.4 years◦ Males/females: 10/5	Level of injury: T8–L2	<ul style="list-style-type: none">• Early surgery group: ≤8 h• Late surgery group: 3 to 15 days	AIS, GCS, LOS, and complications.	<ul style="list-style-type: none">• Both groups were comparable regarding AIS (<i>p</i> = 0.9), and type of fracture (<i>p</i> ≥ 0.05).• Postoperative AIS significantly increased from the pre-operative AIS in the early surgery group (<i>p</i> = 0.004) and in the late surgery group (<i>p</i> = 0.046), but post-operative AIS of the early surgery group was better than the late surgery group (<i>p</i> < 0.011).• However, 83.3% of individuals in the early surgery group showed improvement in the AIS, whereas only 26.6% in the late surgery group improved their AIS.• Early surgery group had no complications, whereas the late surgery group had three cases of lung failure and one case of sepsis. There were no deaths in both groups.	2b	25	

(Continued)

TABLE 2. CONTINUED

Reference	Inclusion and exclusion criteria	Study population	Injury features	Timing of intervention	Outcome measures	Study conclusions	Level of evidence	Quality assessment
Chen et al. (2009)	<ul style="list-style-type: none"> Patients with traumatic cervical SCI who developed central cord syndrome were included. Patients who had associated severe head, severe nerve, severe extremity injury, died before follow-up, lost to follow-up, or had incomplete data were excluded. 	<ul style="list-style-type: none"> N = 49 Age = 55.9 years Males/females = 40/9 N (early surgery group) = 21 N (late surgery group) = 28 	Cause of injury: <ul style="list-style-type: none"> MVA = 29 Fall = 16 Sports injury = 3 Other = 1 	<ul style="list-style-type: none"> Early surgery group: ≤ 4 days. Late surgery group: > 4 days. 	ASIA motor score	<ul style="list-style-type: none"> Early surgery group had significantly shorter LOS in the hospital ($p < 0.001$) and ICU ($p = 0.005$) than the late surgery group. Both early and late surgery groups had similar ASIA motor scores in the final follow-up (88.7 vs. 90.3, respectively). 	4	16

SCI, spinal cord injury; DVT, deep venous thrombosis; UTI, urinary tract infection; ASIA, American Spinal Injury Association; AIS, ASIA impairment scale; LOS, length of stay; ISS, injury severity score; FIM, functional independence measure; ICU, intensive care unit; GCS, Glasgow coma score; MPSS, methylprednisolone; MVA, motor vehicle accident.

for the secondary search. Of the 38 original articles pre-selected from both primary and secondary searches, 22 clinical studies fulfilled the inclusion and exclusion criteria (Botel et al., 1997; Campagnolo et al., 1997; Cengiz et al., 2008; Chen et al., 2009; Chipman et al., 2004; Clohisy et al., 1992; Croce et al., 2001; Duh et al., 1994; Guest et al., 2002; Kerwin et al., 2005; Kregel et al., 1993; Levi et al., 1991; McKinley et al., 2004; McLain and Benson, 1999; Mirza et al., 1999; Ng et al., 1999; Papadopoulos et al., 2002; Pollard and Apple, 2003; Sapkas and Papadakis, 2007; Schinkel et al., 2006; Tator et al., 1999; Vaccaro et al., 1997). Extracted data from those clinical studies are summarized in Table 2. Most of the clinical studies compared at least two patient groups who underwent early or later decompressive operation of spinal cord ($n = 20$); the two studies examined only the feasibility and safety of early surgical decompression of spinal cord without group comparisons (Botel et al., 1997; Tator et al., 1999). While the vast majority of the clinical studies were level-4 evidence, there were two studies of level-2b evidence (Table 2). The quality assessment scores varied from 7 to 25 with a mean value of 12.41 and a median value of 11.5.

Focused questions

Pre-clinical studies. Although a number of pre-clinical studies suggest no effects of time of spinal cord compression on outcomes, several other experimental investigations indicate that longer spinal cord compression is associated with detrimental effects in animal SCI models. In addition, the three pre-clinical studies that used a single time period of spinal cord compression also showed the histopathological, electrophysiological, and blood flow effects of mechanical compression of spinal cord tissue (Bohlman et al., 1979; Brodkey et al., 1972; Koberne et al., 1978).

Negative results were reported in pre-clinical studies that used diverse animal SCI models. Using a weight holding device, Croft et al. (1972) studied 15 cats that underwent spinal cord compression of different weights (18 to 58 g) at different time periods from 5 to 20 min. While greater weights produced more severe locomotor deficits and electrophysiological changes, no substantial effect of time of spinal cord compression was reported, but data were not statistically analyzed (Croft et al., 1972). Thienprasit et al. (1975) used an epidural balloon for rapid spinal cord compression followed by immediate release in cats that were subsequently classified according to electrophysiological recovery within the first 6 h post-SCI. Among animals that had no cortical evoked potentials after 6 h of SCI, there were no significant differences between the group of animals that underwent spinal cord decompression at 6 h after SCI and the group of untreated animals, but laminectomy at 6 h and subsequent spinal cord cooling resulted in improved behavioral outcome when compared to untreated animals and laminectomy-alone animals (Thienprasit et al., 1975). Among those animals that showed some electrophysiological recovery within the first 6 h post-SCI, there were no significant differences between the group of animals that underwent laminectomy only at 6 h and the group of animals that underwent laminectomy at 6 h with subsequent spinal cord cooling (Thienprasit et al., 1975). Using a spinal cord compression model, Aki and Toya (1984) reported that the weight applied to the spinal cord was significantly associated with electrophysiological changes, his-

topathological findings, and blood flow disturbances; whereas, there were no significant differences between the group of animals that received 30-min compression and the group of animals that underwent 60-min compression with regard to spinal cord blood flow alterations. Studying the effects of circumferential compression of caudal equina (from 2–3 sec to 1 week) in dogs, Delamarter et al. (1991) documented no significant effects of time of compression on electrophysiological, histopathological, and behavioral results. More recently, Hejcl et al. (2008) reported that delayed implantation (at 1 week after injury) of hydrogel between the stumps of transected spinal cord did not adversely affect histopathological and behavioral outcomes in comparison with implantation of hydrogel immediately after spinal cord transection. Of note, both implantation groups showed significantly reduced lesion volume when compared with control animals (Hejcl et al., 2008).

In contrast, numerous pre-clinical studies using different SCI models reported the benefits of short spinal cord compression or early spinal cord decompression. Using an epidural balloon compression model, Koberne et al. (1979) found that monkeys with 1-min spinal cord compression showed better electrophysiological recovery and reduced adverse effects on spinal cord blood flow in comparison with animals that underwent spinal cord compression for 3 to 15 min. Studying rats that underwent spinal cord clip compression of 16 to 178 g for 3 to 900 sec, Dolan et al. (1980) documented a significant correlation between behavioral recovery and time of spinal cord compression. Guha et al. (1987) also reported behavioral outcomes in rats that underwent a clip compression of 2.3 or 16.9 g depended upon the time of compression, which varied from 15 to 240 min. Similarly, Nystrom and Berglund (1988) documented time-dependent differences in behavioral outcomes in rats using a spinal cord compression model of 20 to 50 g for 1 to 10 min. Zhang et al. (1993) found significant elevation of spinal cord concentrations of energy-related metabolites in rats that underwent spinal cord compression of 9 to 50 g for 5 min in comparison with control animals without SCI. Using a circumferential spinal cord compression model in dogs, Delamarter et al. (1995) reported time-related effects on electrophysiological recovery (worsening from 2–3 sec to 1 h or longer), behavioral recovery and histopathological lesion (worsening with compression of 6 h or longer). Studying the effects of spinal cord compression that reduced approximately 50% of the somatosensory-evoked potentials in dogs, Carlson et al. (1997b) found significant differences between the group of animals that received 5-min compression and the group of animals that underwent 3-h compression regarding electrophysiological recovery and spinal cord blood flow recovery. In another study using a similar animal SCI model as previously described, Carlson et al. (1997a) reported that dogs recovered only some degree of electrophysiological deficit and reperfusion flow when the spinal cord was decompressed at 3 h in comparison with animals that had spinal cord decompression at 30 min or at 1 h. Using a spinal cord compression-contusion model in rats, Dimar et al. (1999) documented time dependence of spinal cord compression with regard to electrophysiological recovery (immediate decompression versus 2-h compression), histopathological findings (2-h vs. 6-h compression), and behavioral recovery at 6 weeks after SCI (Dimar et al., 1999). In dogs that underwent spinal cord

compression using a loading device, Carlson et al. (2003) showed that animals with 30-min compression had improved electrophysiological recovery, reduced histopathological lesion, and improved behavioral recovery when compared with animal with 3-h compression. Most recently, Rabinowitz et al. (2008) conducted a randomized prospective study in dogs comparing early surgical decompression (6 h) with or without methylprednisolone compared to methylprednisolone alone. Using a model originally described by Delamarter et al. (1995) a single surgeon carried out a laminectomy at the L 4/5 level (equivalent to the thoracolumbar junction in humans) and circumferentially compressed the dura by 60% with a nylon band. The surgical wound was then closed and the animals lifted from anesthesia (the nylon band was left *in situ*). The animals were then randomized to one of three groups (methylprednisolone + early decompressive surgery, saline + early decompressive surgery, or methylprednisolone only). Medical therapy with methylprednisolone or saline was initiated 1 h after the lesion-inducing surgery. Decompressive surgery was carried out 6 h following the initial insult by taking the animals back to the operating room and removing the nylon band. The animals randomized to not receive decompressive surgery had the band in place for the duration of the experiment. The animals were followed clinically and electrophysiologically for 2 weeks at which point they were sacrificed and examined histologically. The authors demonstrated that surgical decompression with or without methylprednisolone administration offers greater neurological improvement than the use of methylprednisolone alone. This is an important study that compared two therapies at the forefront of human treatment that had yet to be compared head-to-head. The authors rightfully comment on the value of such a trial.

Clinical studies. The definitions of early surgical intervention in patients with traumatic SCI varied from 8 h to 4 days in clinical studies. In addition, delayed surgical decompression of spinal cord was more inconsistently defined in the literature with time threshold varying from 8 h to 5 days. While 8 out of 22 clinical studies defined early surgical intervention as spinal cord decompression and stabilization obtained prior to 72 h following traumatic SCI (Chipman et al., 2004; Croce et al., 2001; Kerwin et al., 2005; McKinley et al., 2004; Mirza et al., 1999; Sapkas and Papadakis, 2007; Schinkel et al., 2006; Vaccaro et al., 1997), 9 other clinical investigations employed the 24-h limit to define early decompressive operation (Botel et al., 1997; Campagnolo et al., 1997; Duh et al., 1994; Guest et al., 2002; Krenzel et al., 1993; Levi et al., 1991; McLain and Benson, 1999; Pollard and Apple, 2003; Tator et al., 1999). Other thresholds have been utilized in some previous clinical studies that compared delayed surgical intervention with spine operations earlier than 8 h (Cengiz et al., 2008; Ng et al., 1999), 48 h (Clohisey et al., 1992), and 4 days (Chen et al., 2009). One study did not specify a time frame but did state emergent decompression (Papadopoulos et al., 2002).

In two previous studies, patients who underwent spinal cord decompression within the first 8 h after traumatic SCI were found to have shorter hospitalization, shorter length of stay in the acute care unit, less frequent secondary complications post-trauma, and better neurological outcomes than patients who were operated later than 8 h post-injury (Table 2). However, one study reported no differences between those patient groups in terms of mortality after SCI (Table 2).

Surgical intervention of spinal cord injury earlier than 24 h was associated with shorter length of hospitalization in three studies, shorter length of stay in the intensive care unit in one study, better neurological recovery in one study, and smaller estimated blood loss for anterior procedures in one study (Table 2). In contrast, no effects of early surgical intervention (≤ 24 h) were documented in previous studies with regard to the frequency of secondary complications after SCI (two studies), neurological outcomes (four studies), or estimated blood loss for anterior procedures (one study) (Table 2).

In only one prior study, patients who underwent anterior decompression of the spinal cord earlier than 48 h had better neurological recovery in comparison with patients who were surgically treated after 48 h of traumatic SCI (Table 2) (Clohisey et al., 1992).

Early surgical operation, defined by a cutoff of 72 h, was associated with shorter length of hospital stay in six previous studies, shorter length of stay in the intensive care unit in three studies, smaller volume of fresh frozen plasma during operation in one study, lower mortality rate in one study, lower frequency of secondary complications after SCI in six studies, better neurological recovery in one study, and less costly care in two studies when compared with delayed operation (Table 2). However, patients who underwent early surgical decompression and stabilization of the spinal cord (≤ 72 h) did not differ from patients who were surgically treated after 72 h with regard to length of hospitalization (two studies), length of stay in the acute care unit (three studies), intraoperative volume of crystalloid reposition (one study), frequency of secondary complications after SCI (four studies), mortality (three studies), neurological outcome (three studies), rehospitalization (one study), and disability (three studies) (Table 2).

In one previous study, patients who underwent surgical intervention within the first 4 days after SCI showed similar neurological recovery to patients who were surgically treated earlier than 4 days (Table 2).

Discussion

This systematic review identified 19 pre-clinical studies in which timing of spinal cord compression or decompression was examined using animal SCI models. Despite some discrepancies in the results of those pre-clinical studies, there is evidence for a biological rationale to support early decompression of the spinal cord. In addition, our systematic review captured 22 clinical studies that examined either the feasibility and safety or efficacy of early surgical intervention to stabilize and align the spine and decompress the spinal cord. The most common definitions of early surgical intervention included 24 or 72 h after SCI as the cutoff time. A number of studies indicated that patients who undergo early surgical decompression can have similar outcomes to patients who received delayed decompressive operation. However, there is evidence to suggest that early surgical intervention is safe and feasible and that it can improve clinical and neurological outcomes and reduce health care costs.

Is there pre-clinical evidence for biological benefits of early surgical decompression in animal SCI models?

In our systematic review, 5 of 19 pre-clinical studies suggested that time has little or no effect on outcomes in animal

SCI models, whereas 11 other pre-clinical investigations indicated a time-dependent effect of spinal cord compression in the behavioral recovery, spinal cord blood flow disturbances, electrophysiological recovery, and histopathological lesion. All pre-clinical studies captured in our review were *in vivo* experiments that used different SCI models of spinal cord contusion or compression. In addition to rodents, those prior experimental studies also included cats, dogs, and monkeys. Generally speaking, the benefits of spinal cord decompression in those animal studies appear to be optimized when blood flow and electrophysiological parameters were restored earlier than 6 h; however, this did depend on the model of SCI, animal species or strain, methodological quality, outcome measure, use of anesthesia, and time period of follow-up (Akhtar et al., 2009). The critical analysis of the current pre-clinical evidence strongly indicated that time of spinal cord compression is a key determinant of recovery after SCI and, hence, there is a biological rationale to support early spinal cord compression for improved outcomes.

What is the optimal timing for surgical decompression of spinal cord based on the current clinical evidence?

The safety and feasibility of early spine intervention after SCI were examined in at least two level-4 evidence studies (Botel et al., 1997; Tator et al., 1999). Both clinical studies indicated that between 23.5% and 51.4% of the patients could undergo operation within the first 24 h after acute SCI. One may speculate that modifications of the pre-hospital logistics and acute SCI care could substantially increase the number of patients who would undergo operation earlier than 24 h after acute traumatic SCI.

In the literature, the most commonly used timelines to define "early surgical intervention of spine" were 24 and 72 h in studies of level-4 evidence. The results of those studies were consistent with either no effect of timing of surgical intervention on outcomes after SCI (no harm was reported in the early surgery groups) or improved outcomes when earlier surgical treatment was performed. There was one level-2b evidence study that indicated no benefits regarding clinical and neurological outcomes between the group of patients who underwent surgical decompression of spinal cord within the first 72 h after cervical SCI ($n = 34$) and the group of patients who were surgically treated later than 72 h post-injury ($n = 28$) (Vaccaro et al., 1997). The relatively small sample sizes of each study group raise the possibility of an underpowered statistical analysis in that prospective cohort study. In addition, another level-2b evidence study suggested that surgical decompression and stabilization of spinal cord earlier than 8 h would provide better neurological outcome, shorter length of hospitalization, shorter length of stay in the intensive care unit, and lower frequency of secondary complications in comparison with patients who underwent surgical intervention from 72 h to 5 days after thoracolumbar SCI (Cengiz et al., 2008).

Despite the lack of definite substantiation for one particular timeline, the current clinical evidence along with data from pre-clinical studies suggest that outcomes after traumatic SCI would be potentially optimized if surgical decompression and stabilization of spinal cord were carried out between 8 and 24 h.

What are the potential effects of early decompression of spinal cord on the clinical, neurological, and functional outcomes in the acute care setting?

In addition to being safe and feasible in many cases, early surgical decompression (≤ 24 h) has the potential to reduce surgical blood loss, decrease the volume of fresh frozen plasma required during operation, reduce the length of hospitalization, decrease the length of stay in the intensive care unit, improve neurological outcome, and reduce the number of secondary complications after traumatic SCI. While those results on clinical and neurological outcomes were based on a number of level-4 evidence and one clinical study of level-2b evidence, other prior level-4 evidence studies and another level-2b study have challenged those positive effects with regard to reduced number of secondary complications and improved neurological outcomes after early surgical intervention.

Similarly, several prior level-4 evidence studies indicated that surgical intervention earlier than 72 h could reduce length of hospitalization, decrease length of stay in the intensive care, reduce surgical blood loss, decrease the volume of fresh frozen plasma required during operation, improve neurological outcome, reduce acute care costs, and increase survival after traumatic SCI. However, a number of other level-4 evidence studies indicated no differences between a group of patients who underwent early operation and a group of patients surgically treated later than 72 h with regard to length of hospitalization, length of stay in the intensive care, volume of crystalloids required during operation, number of secondary complications, survival, neurological and functional recovery, and need for re-hospitalization.

Although prior studies failed to consistently support better clinical, neurological, and functional outcomes in the early surgery group, there is strong evidence to support that early surgical decompression of spinal cord does not increase the risk of treatment harm in patients with acute traumatic SCI. Moreover, the potential to improve outcomes in the group of patients who undergo early surgical intervention is congruent with the biological rationale supported by the pre-clinical literature.

Of note, the preliminary results from the Surgical Treatment for Acute Spinal Cord Injury Study (STASCIS) also suggest that decompression of the spinal cord earlier than 24 h from injury is associated with improved neurological recovery in patients with isolated cervical SCI (Fehlings and Arvin, 2009). Definite results of this large multicenter prospective cohort study are anticipated in the coming year after completion of data acquisition from long-term follow-up.

Recommendations

In the modified Delphi process, a panel of 10 experts in the field of SCI endorsed the following recommendations:

1. There is strong pre-clinical evidence for biological benefits of early surgical decompression in animal SCI models.
2. It is recommended that surgical decompression of the injured spinal cord be performed within 24 h when medically feasible. The optimal timing of surgical decompression, or whether surgery is indicated at all, in patients with a central cord injury remains unclear.
3. There are clinical, neurological, and functional benefits of early decompression of the spinal cord.

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